High Impact Publications with the HALO® Image Analysis Platform

Digital pathology with the HALO® image analysis platform continues to advance research across areas including immunology, infectious disease, immuno-oncology, and neuroscience. Here, we list recent high-impact publications and explore several applications in detail.

Although some publications could have been placed into multiple categories, they are only listed once. Check any related categories for additional publications in your research area.

Infectious Disease

Deng W, Bao L, Song Z *et al*. Infection with SARS-CoV-2 can cause pancreatic impairment. *Sig Transduct Target Ther* **9**: 98 (2024). DOI: 10.1038/s41392-024-01796-2.

Palmer CS, Perdios C, Abdel-Mohsen M *et al*. Non-human primate model of long-COVID identifies immune associates of hyperglycemia. *Nat Commun* **15**: 6664 (2024). DOI: 10.1038/s41467-024-50339-4.

Indoleamine-2,3-dioxygenase inhibition improves immunity and is safe for concurrent use with cART during Mtb/SIV coinfection

Authors: Singh B, Sharan R, Ravichandran G, Escobedo R, Shivanna V, Dick Jr. EJ, Hall-Ursone S, Arora G, Alvarez X, Singh DK, Kaushal D, Mehra S

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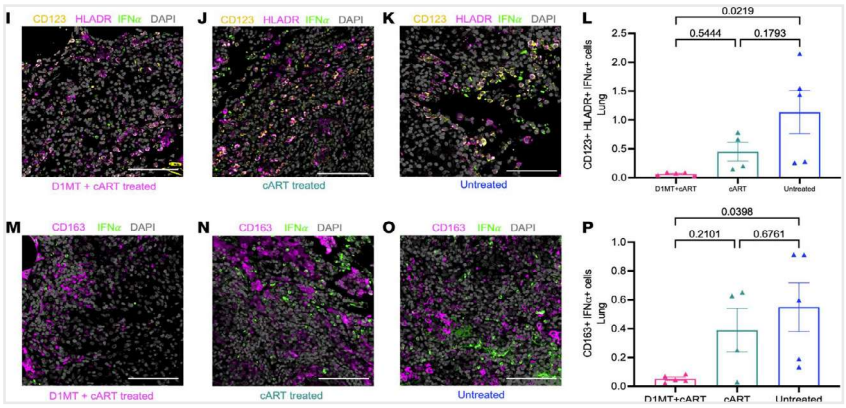

Science: People living with HIV are more likely to suffer from reactivation of latent tuberculosis infection (LTBI) than individuals with LTBI alone, with chronic immune activation being a likely driving factor. Human TB granulomas exhibit elevated levels of myeloid cells expressing indoleamine 2,3, dioxygenase (IDO). IDO expression alters T cell proliferation, promotes immunosuppression, and has been correlated with chronic immune activation and risk for TB reactivation in non-human primate (NHP) models of TB/SIV coinfection. Bindu Singh and coauthors sought to expand understanding of the effect and therapeutic potential of IDO inhibition by investigating combined IDO inhibition and combinatorial antiretroviral therapy (cART) in NHP TB/SIV coinfection. The authors found that joint IDO inhibition/cART resulted in decreased chronic immune activation and promoted adaptive anti-TB responses. Additionally, the combined treatment suppressed SIV replication to the same level as cART monotherapy and did not affect lung pathology.

Technology: Macrophages, pDCs, CD4+ T cells, CD8+ T cells, and cells expressing IFN-α, PD-1, PD-L1, or IDO were quantified in FFPE NHP lung sections using the HALO Highplex FL module. The feature image shows IFN-α+ pDC and macrophage in the lungs of treated and untreated animals and their quantification. To measure lung pathology, inflamed or granulomatous area in primate lungs was quantified using a tissue classifier developed with the Tissue Classifier Add-on and trained on H&E-stained lung sections.

Oncology and Immuno-oncology

Ahn DH, Ridinger M, Cannon TL *et al.* Onvansertib in Combination With Chemotherapy and Bevacizumab in Second-Line Treatment of *KRAS*-Mutant Metastatic Colorectal Cancer: A Single-Arm, Phase II Trial. *J Clin* Onc **43(7)**: 840-851 (2025). DOI: 10.1200/JCO-24-01266.

An M, Mehta A, Min BH *et al.* Early Immune Remodeling Steers Clinical Response to First-Line Chemoimmunotherapy in Advanced Gastric Cancer. *Cancer Discov* **14(5)**: 766-785 (2024). DOI: 10.1158/2159-8290.CD-23-0857.

Chapeau EA, Sansregret L, Galli GG *et al.* Direct and selective pharmacological disruption of the YAP–TEAD interface by IAG933 inhibits Hippo-dependent and RAS–MAPK-altered cancers. *Nat Cancer* **5**: 1102–1120 (2024). DOI: 10.1038/s43018-024-00754-9.

Duan H, Shao C, Luo Z *et al.* Perioperative sintilimab and neoadjuvant anlotinib plus chemotherapy for resectable non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 2 trial (TD-NeoFOUR trial). *Sig Transduct* Target *Ther* **9**: 296 (2024). DOI: 10.1038/s41392-024-01992-0.

Adjuvant COX inhibition augments STING signaling and cytolytic T cell infiltration in irradiated 4T1 tumors

Authors: Ridnour LA, Cheng RYS, Kedei N, Somasundaram V, Bhattacharyya DD, Basudhar D, Wink AL, Walke AJ, Kim C, Heinz WF, Edmondson EF, Butcher DO, Warner AC, Dorsey TH, Pore M, Kinders RJ, Lipkowitz S, Bryant RJ, Rittscher J, Wong STC, Hewitt SM, Chang JC, Shalaby A, Callagy GM, Glynn SA, Ambs S, Anderson SK, McVicar DW, Lockett SJ, Wink DA

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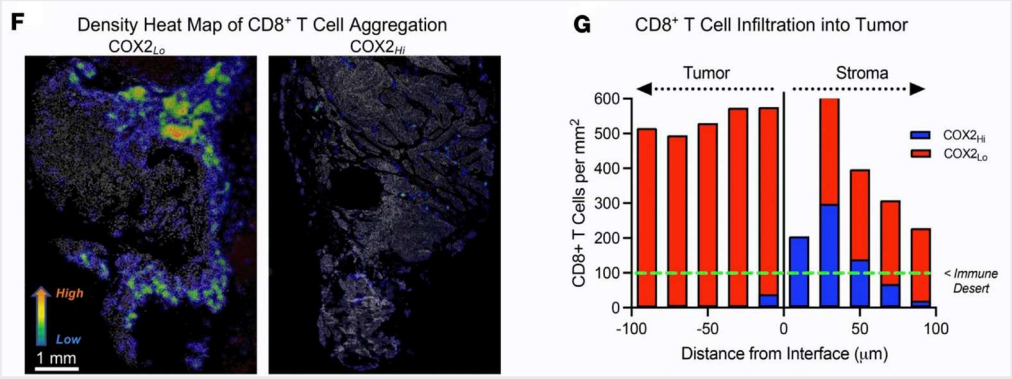

Science: The inducible forms of nitric oxide synthase (NOS2) and cyclooxygenase-2 (COX2) modulate inflammation in the tumor microenvironment (TME), and high NOS2 and COX2 expression predict poor survival in patients with estrogen receptor-negative or triple-negative breast cancer (TNBC). Lisa Ridnour and coauthors investigated the correlation between COX2 levels and immune cell localization as well as the potential for improving the efficacy of radiation therapy in TNBC through adjuvant pan-NOS or -COX inhibition. The authors observed that $COX2_{lo}$ TNBC tumors exhibited markedly higher CD8+ T cell infiltration. They subsequently showed in the murine 4T1 TNBC tumor model that combining radiation therapy with COX inhibition reduced primary tumor growth and metastasis, lengthened median survival, and increased tumor infiltration of CD8+ and CD4+ T cells. These results support clinically available COX-inhibiting NSAIDs as a promising adjuvant with radiation therapy for treatment of tumors expressing high levels of COX2.

Technology: Differences in the spatial distribution of immune cells in $COX2_{lo}$ and $COX2_{hi}$ TNBC patient tumor samples were observed by first manually annotating tumor, stroma, and necrosis regions on H&E-stained slides before images were registered and fused with multiplex immunofluorescent images. The HALO Highplex FL module was then used to phenotype and quantify immune cells, while the Spatial Analysis module was used to generate CD8+ T cell heatmaps and measure tumor infiltration based on the annotations, as shown in the feature image. To investigate T cell polarization, the HALO FISH module was used to analyze expression of Granzyme B, IFN-γ, and IL-10, while viable and necrotic tumor regions were classified in each sample with the Tissue Classifier Add-on.

Elbatsh AMO, Amin-Mansour A, Haberkorn A *et al*. INPP5A phosphatase is a synthetic lethal target in GNAQ and GNA11-mutant melanomas. *Nat Cancer* **5**: 481–499 (2024). DOI: 10.1038/s43018-023-00710-z.

Ferretti S, Hamon J, de Kanter R *et al*. Discovery of WRN inhibitor HRO761 with synthetic lethality in MSI cancers. *Nature* **629**: 443–449 (2024). DOI: 10.1038/s41586-024-07350-y.

Friedman CF, Manning-Geist BL, Zhou Q *et al*. Nivolumab for mismatch-repair-deficient or hypermutated gynecologic cancers: a phase 2 trial with biomarker analyses. *Nat Med* **30**: 1330–1338 (2024). DOI: 10.1038/s41591-024-02942-7.

Gu L, Peng C, Liang Q *et al*. Neoadjuvant toripalimab plus axitinib for clear cell renal cell carcinoma with inferior vena cava tumor thrombus: NEOTAX, a phase 2 study. *Sig Transduct Target Ther* **9**: 264 (2024). DOI: 10.1038/s41392-024-01990-2.

Gulla A, Morelli E, Johnstone M *et al.* Loss of GABARAP mediates resistance to immunogenic chemotherapy in multiple myeloma. *Blood* **143(25)**: 2612-2626 (2024). DOI: 10.1182/blood.2023022777.

Hughes D, Evans A, Go S *et al.* Development of human pancreatic cancer avatars as a model for dynamic immune landscape profiling and personalized therapy. *Sci Adv* **10(27)**: eadm9071 (2024). DOI: 10.1126/sciadv.adm9071.

Jiang J, Jiang L, Maldonato BJ *et al.* Translational and Therapeutic Evaluation of RAS-GTP Inhibition by RMC-6236 in RAS-Driven Cancers. *Cancer Discov* **14(6)**: 994-1017 (2024). DOI: 10.1158/2159-8290.CD-24-0027.

Malla SB, Byrne RM, Lafarge MW *et al*. Pathway level subtyping identifies a slow-cycling biological phenotype associated with poor clinical outcomes in colorectal cancer. *Nat Genet* **56:** 458–472 (2024). DOI: 10.1038/s41588-024-01654-5.

Quinlan JA, Inglut CT, Srivastava P *et al.* Carrier-Free, Amorphous Verteporfin Nanodrug for Enhanced Photodynamic Cancer Therapy and Brain Drug Delivery. *Adv Sci* **11(17)**: (2024). DOI: 10.1002/advs.202302872.

Sun CM, Toulmonde M, Spalato-Ceruso M *et al*. Impact of metronomic trabectedin combined with low-dose cyclophosphamide on sarcoma microenvironment and correlation with clinical outcome: results from the TARMIC study. *Mol Cancer* **23**: 37 (2024). DOI: 10.1186/s12943-024-01942-y.

Thatikonda V, Lyu H, Jurado S *et al*. Co-targeting SOS1 enhances the antitumor effects of $KRAS^{G12c}$ inhibitors by addressing intrinsic and acquired resistance. *Nat Cancer* **5**: 1352–1370 (2024). DOI: 10.1038/s43018-024-00800-6.

Verschoor YL, van de Haar J, van den Berg JG *et al*. Neoadjuvant atezolizumab plus chemotherapy in gastric and gastroesophageal junction adenocarcinoma: the phase 2 PANDA trial. *Nat Med* **30**: 519–530 (2024). DOI: 10.1038/s41591-023-02758-x.

Wasko UN, Jiang J, Dalton TC *et al*. Tumour-selective activity of RAS-GTP inhibition in pancreatic cancer. *Nature* **629**: 927–936 (2024). DOI: 10.1038/s41586-024-07379-z.

Yang Y, Chen X, Pan J *et al*. Pan-cancer single-cell dissection reveals phenotypically distinct B cell subtypes. *Cell* **187(17)**: 4790-4811 (2024). DOI: 10.1016/j.cell.2024.06.038.

Yang Z, Gao J, Zheng J *et al*. Efficacy and safety of PD-1 blockade plus long-course chemoradiotherapy in locally advanced rectal cancer (NECTAR): a multi-center phase 2 study. *Sig Transduct Target Ther* **9**: 56 (2024). DOI: 10.1038/s41392-024-01762-y.

Yang Z, Wang X, Fu Y *et al*. YTHDF2 in peritumoral hepatocytes mediates chemotherapy-induced antitumor immune responses through CX3CL1-

mediated CD8+ T cell recruitment. *Mol Cancer* **23**: 186 (2024). DOI: 10.1186/s12943-024-02097-6.

Zheng H, An M, Luo Y *et al.* PDGFRα+ITGA11+ fibroblasts foster early-stage cancer lymphovascular invasion and lymphatic metastasis via ITGA11-SELE interplay. *Cancer Cell* **42(4)**: 682-700 (2024). DOI: 10.1016/j.ccell.2024.02.002.

Fibrosis

Mayr CH, Santacruz D, Jarosch S *et al.* Spatial transcriptomic characterization of pathologic niches in IPF. *Sci Adv* **10(32)**: eadl5473 (2024). DOI: 10.1126/sciadv.adl5473.

Ren F, Aliper A, Chen J *et al.* A small-molecule TNIK inhibitor targets fibrosis in preclinical and clinical models. *Nat Biotechnol* **43**: 63–75 (2025). DOI: 10.1038/s41587-024-02143-0.

Heteroduplex oligonucleotide technology boosts oligonucleotide splice switching activity of morpholino oligomers in a Duchenne muscular dystrophy mouse model

Authors: Hasegawa J, Nagata T, Ihara K, Tanihata J, Ebihara S, Yoshida-Tanaka K, Yanagidaira M, Ohara M, Sasaki A, Nakayama M, Yamamoto S, Ishii T, Iwata-Hara R, Naito M, Miyata K, Sakaue F, Yokota T

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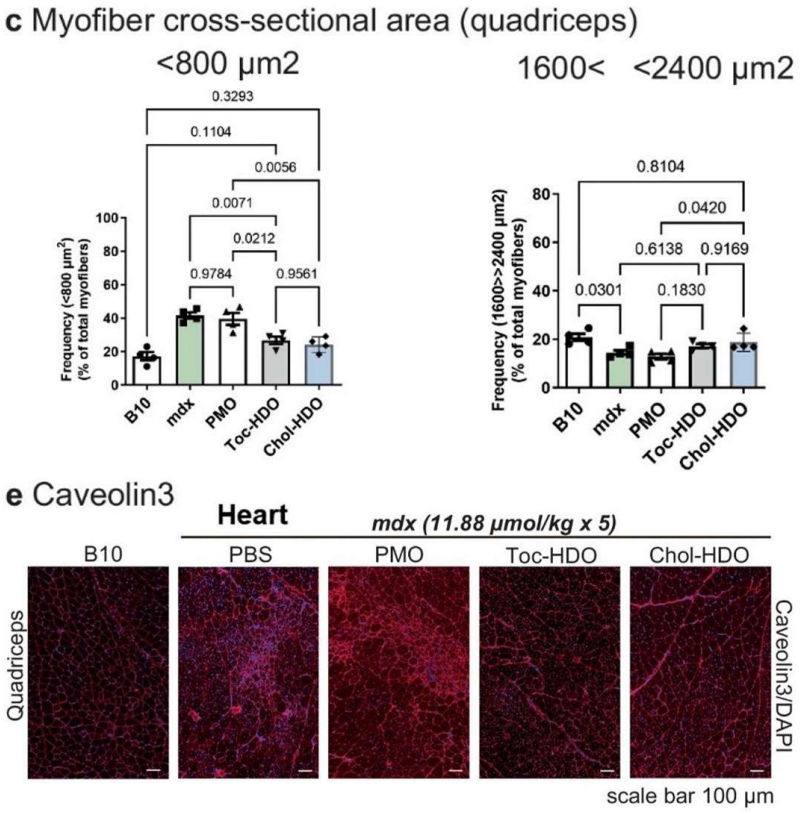

Science: Duchenne muscular dystrophy (DMD), the most common form of myopathy, results from an absence or large reduction in dystrophin caused by mutations in the coding exons. While no cure exists for DMD, splice-switching oligonucleotides are a promising area of research in DMD treatment. These drugs promote the skipping of exons with frame-shift mutations to yield in-frame, functional dystrophin with an internal deletion. Juri Hasegawa and coauthors sought to improve the suboptimal tissue uptake of phosphorodiamidate morpholino oligomers (PMO), a type of exon-skipping therapy, by incorporating them in cholesterol- or tocopherol-conjugated heteroduplex oligonucleotides (HDO). The authors demonstrated that PMO/HDO had significantly increased tissue uptake compared to PMO in a mdx mouse model of DMD and caused a significant increase in dystrophin expression. Critically, treatment with PMO/HDO normalized motor function, muscle pathology, and cardiac and CNS abnormalities in mdx mice.

Technology: To observe potential changes in muscle fiber histology following PMO/HDO treatment, the myofiber cross-sectional area (CSA) and percent of centrally-nucleated fibers (CNF) were measured using the HALO Muscle Fiber FL module. The feature image shows the results of CSA and CNF quantification in quadriceps femoris sections, as well as representative section images. Separately, cardiac fibrosis was quantified as an indicator of cardiomyopathy, with the HALO Area Quantification BF module used to measure fibrotic area in transverse mdx mouse heart sections after staining with Masson's trichrome.

Yang X, Lin G, Chen Y *et al*. Chlorquinaldol Alleviates Lung Fibrosis in Mice by Inhibiting Fibroblast Activation through Targeting Methionine Synthase Reductase. *ACS Cent Sci* **10(9)**: 1789–1802 (2024). DOI: 10.1021/acscentsci.4c00798.

Immunology

Fang Q, Chen X, Cao F *et al*. SPHK1 promotes HNSCC immune evasion by regulating the MMP1-PD-L1 axis. *Theranostics* **14(18)**: 7199-7218 (2024). DOI: 10.7150/thno.102390.

Guo CL, Wang CS, Wang ZC *et al.* Granzyme $K^{+}CD8^{+}$ T cells interact with fibroblasts to promote neutrophilic inflammation in nasal polyps. *Nat Commun* **15**: 10413 (2024). DOI: 10.1038/s41467-024-54685-1.

Huang D, Liu X, Gao X *et al.* Meteorin-like protein/METRNL/Interleukin-41 ameliorates atopic dermatitis-like inflammation. *Allergy* **80(2)**: 474-488 (2024). DOI: 10.1111/all.16150.

Lemos MP, Astronomo RD, Huang Y *et al.* Enhanced and sustained biodistribution of HIV-1 neutralizing antibody VRC01LS in human genital and rectal mucosa. *Nat Commun* **15**: 10332 (2024). DOI: 10.1038/s41467-024-54580-9.

Muckenhuber M, Mengrelis K, Weijler AM *et al.* IL-6 inhibition prevents costimulation blockade-resistant allograft rejection in T cell-depleted recipients by promoting intragraft immune regulation in mice. *Nat Commun* **15**: 4309 (2024). DOI: 10.1038/s41467-024-48574-w.

Zhu HX, Yang SH, Gao CY *et al.* Targeting pathogenic CD8+ tissue-resident T cells with chimeric antigen receptor therapy in murine autoimmune cholangitis. *Nat Commun* **15**: 2936 (2024). DOI: 10.1038/s41467-024-46654-5.

Neuroscience

Gruber RC, Wirak GS, Blazier AS *et al*. BTK regulates microglial function and neuroinflammation in human stem cell models and mouse models of multiple sclerosis. *Nat Commun* **15**: 10116 (2024). DOI: 10.1038/s41467-024-54430-8.

Lim H, Zhang Y, Peters C *et al.* Genetically- and spatially-defined basolateral amygdala neurons control food consumption and social interaction. *Nat Commun* **15**: 6868 (2024). DOI: 10.1038/s41467-024-50889-7.

Tsartsalis S, Sleven H, Fancy N *et al*. A single nuclear transcriptomic characterisation of mechanisms responsible for impaired angiogenesis and blood-brain barrier function in Alzheimer's disease. *Nat Commun* **15**: 2243 (2024). DOI: 10.1038/s41467-024-46630-z.

Wachter A, Woodbury ME, Lombardo S *et al*. Landscape of brain myeloid cell transcriptome along the spatiotemporal progression of Alzheimer's disease reveals distinct sequential responses to Aβ and tau. *Acta Neuropathol* **147**: 65 (2024). DOI: 10.1007/s00401-024-02704-2.

Xu H, Qiu Q, Hu P *et al*. MSUT2 regulates tau spreading via adenosinergic signaling mediated ASAP1 pathway in neurons. *Acta Neuropathol* **147**: 55 (2024). DOI: 10.1007/s00401-024-02703-3.

Additional Research Areas

Fu Y, Ding X, Zhang M *et al*. Intestinal mucosal barrier repair and immune regulation with an AI-developed gut-restricted PHD inhibitor. *Nat Biotechnol* (2024). DOI: 10.1038/s41587-024-02503-w.

Kiourtis C, Terradas-Terradas M, Gee LM *et al*. Hepatocellular senescence induces multi-organ senescence and dysfunction via TGFβ. *Nat Cell Biol* **26**: 2075–2083 (2024). DOI: 10.1038/s41556-024-01543-3.

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